Enteropathies: “When the Mucosa Isn't Working”

Carol E. Semrad, M.D., FACG
Professor of Medicine
The University of Chicago

Enteropathy Definitions

- Any Pathology of the Intestine
- A disease of the Intestinal Tract
- Small Intestinal Diseases associated with Villous Atrophy

Infection and Celiac Disease most common causes in the U.S.
Enteropathy
Clinical Presentation

• Diarrhea
  - gas/Bloating
  - weight loss
  - many vitamin and mineral deficiencies

OR

• No Diarrhea
  - select vitamin/mineral deficiency
  - anemia
  - bone mass loss
  - skin/neurologic symptoms
Case Study

- 59 y.o. Caucasian woman
- 6 mo watery diarrhea, bloating, nausea, vomiting
- 60 pound weight loss
- No travel
- Several ER visits for dehydration
- PMH: Obesity, Depression
- Medications: citalopram, dicyclomine, loperamide, prochlorperazine
- Outside evaluation 3 months prior:
  - Stool Studies: negative
  - Hgb 10.9 g/dl HCT 33% MCV 95
  - EGD: normal duodenum, no biopsy obtained
  - Colonoscopy: random biopsies with mild colitis
  - Abd CT scan, SBFT: normal

Admitted to Hospital, PN started

- Physical Examination:
  - BP 87/50 P 90 Ht 5’ 4” Wt 119 lbs (usual 184lbs)
  - Marked muscle wasting, loose skin, weak
  - Abdomen: benign

- Laboratory Studies:
  - Na 136 Cl 104 mEq/L
  - K 2.9 CO₂ 21
  - BUN 13 CR 1.0 mg/dl
  - Albumin 2.8 TP 5.2 g/dl
  - Abnormal liver tests
  - Decreased folate, Fe, Zn, Cu, vitamin A, E, D levels
  - Normal Vitamin B₁₂ level
Case Study – Synthesis

- Diarrhea with weight loss and multiple vitamin/mineral deficiencies
- Suspected enteropathy
- Vomiting ? gastric involvement (e.g. celiac, refractory celiac, autoimmune)
- Elevated liver tests
  - ? fatty liver of severe malnutrition
  - ? celiac disease

Diseases Associated with Villous Atrophy

<table>
<thead>
<tr>
<th>Examples</th>
<th>Mechanism</th>
<th>Biopsy Specific?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>various organisms</td>
<td>yes</td>
</tr>
<tr>
<td>Giardia, Whipple, AIDs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celiac Disease</td>
<td>gluten</td>
<td>no</td>
</tr>
<tr>
<td>Tropical Sprue</td>
<td>? coliform bacteria</td>
<td>no</td>
</tr>
<tr>
<td>Agammaglobulinemia</td>
<td>lack of plasma cells</td>
<td>yes</td>
</tr>
<tr>
<td>Autoimmune GVHD</td>
<td>crypt apoptosis, no goblets</td>
<td>yes</td>
</tr>
<tr>
<td>Drug</td>
<td>unknown</td>
<td>no</td>
</tr>
<tr>
<td>olmesartan</td>
<td>anti-proliferative</td>
<td>no</td>
</tr>
<tr>
<td>mycophenolate</td>
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<tr>
<td>methotrexate</td>
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</tbody>
</table>
Case Study – Diagnosis

• Further Studies Performed
  - Repeat EGD: duodenal scalloping
  - Duodenal Biopsy:
    Total villous atrophy
    Marked increase in IELs
  - Tissue transglutaminase IgA >100
  - EMA positive

• Diagnosis: Celiac Disease with Crisis

• Started on strict gluten-free diet, budesonide
  • Improvement in diarrhea, vomiting within 2 days
  • Continues to improve off PN and budesonide

Case Pitfalls

• Obtain duodenal biopsy when enteropathy suspected regardless of appearance

• Make diagnosis of enteropathy before severe malnutrition
Celiac Disease
Diagnostic tools

Duodenal biopsy (not specific)

**Antibody**
- TTG IgA, Total IgA
- EMA
- DGP IgG, if IgA deficient

**Genetic Testing**
- HLA DQ2 DQ8
- risk alleles

Celiac Disease – Duodenum

**Endoscopy**
- normal

**Histology**
- Increased IEL (Marsh 1)
- Partial to Total villous atrophy (Marsh 3)

Increased IEL (Marsh 1)
Partial to Total villous atrophy (Marsh 3)
**Duodenal Biopsy**

- Take 4-5 biopsies
- Orientation important for interpretation
- Query for
  - giardia esp. IgA deficiency
  - plasma cells

Lebwohl et al. Gastrointest Endosc 2011;74:103

**Techniques to Improve Endoscopic Detection of Villous Atrophy**

- water emersion
  - quick, simple
  - use power wash
- magnification endoscope “zoom”
  - magnifies image 100-135x
- optical band imaging
  - multiple light wavelengths
  - enhanced image of villi
- confocal endomicroscopy
  - real time histology

Gunther, Daum et al Endoscopy 2010;42:197
Capsule Endoscopy
- 8X Magnification
- High sensitivity for Marsh 3
- Misses Marsh 1
- No biopsy

Petroniene Am J Gastro 2005;100:685
Rondonotti Am J Gastro 2007;102:1624
Hopper Dig Liver Dis 2007;39:140

CD RESPONSE TO A GLUTEN-FREE DIET
70-90% IMPROVE (within 2 weeks)
10-30% FAIL TO IMPROVE Dietary Indiscretion
Wrong Diagnosis
- Missed infections
- Agammaglobulinemia
- Drug
- Tropical Sprue
- Autoimmune, Collagenous

Persistent Villous Atrophy Despite Strictest GFD

Refractory Celiac Disease (RARE ~ 1%)
Refractory Celiac Disease

Persistent Symptoms or Relapse despite a GFD

+  

Strict GF diet

Refractory Celiac Disease: Immunology

- **TYPE I**  
  Polyclonal IEL, most CD8+

- **TYPE II? Early Lymphoma**  
  Aberrant IEL, most CD8-
  T-Cell Receptor γ gene rearrangements

- **DIAGNOSIS – made on Duodenal Biopsy**  
  - Immunohistochemistry formalin-fixed tissue
  - TCR PCR on formalin
  - Flow cytometry on fresh tissue

- ? Cause

**Refractory Celiac Disease Type II**

Immunohistochemistry on Formalin-Fixed Tissue

- **intracellular CD3 Positive**
- **surface CD8 Negative >50%**

Duodenal Biopsy

---

**Problems with T cell Marker Studies**

- Availability of expert Pathologist
- Requires large number of IELs, more biopsies
- Loss of surface markers occurs in a small number of IELs in responsive CD
- No agreement for abnormal
  - ? cut-off % aberrant cells
  - equivocal reports
- False negatives with immunohistochemistry
Refractory Celiac Disease Type II
Additional Findings

• Abdominal CT scan
  - bowel wall thickening
  - lymphadenopathy
  - hyposplenism

• Lymphocytic gastritis
• Ulcerative jejunitis
• T-Cell Lymphoma rare

Further Testing When Refractory Celiac Disease Suspected

• CT/MR Enterography
• Capsule Endoscopy
• Balloon or Spiral Enteroscopy for tissue or retained capsule
• PET Scan if lymphoma suspected

Hadithi et al. World J Gastroenterol 2007;13:1696
Refractory CD - Survival

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient #</th>
<th>5yr Survival</th>
<th>Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netherlands</td>
<td>RCD I 43</td>
<td>96%</td>
<td>0</td>
</tr>
<tr>
<td>2007</td>
<td>RCDII 50*</td>
<td>58%</td>
<td>39*</td>
</tr>
<tr>
<td>France</td>
<td>RCD I 14</td>
<td>93%</td>
<td>2</td>
</tr>
<tr>
<td>2009</td>
<td>RCDII 43</td>
<td>44%</td>
<td>16</td>
</tr>
<tr>
<td>U.S.A.</td>
<td>RCD I 42</td>
<td>80%</td>
<td>0</td>
</tr>
<tr>
<td>2009</td>
<td>RCDII 15</td>
<td>45%</td>
<td>10</td>
</tr>
</tbody>
</table>

*13 with EATL at time of diagnosis

Al-toma et al. Gut 2007;56:1373
Malamut et al. Gastroenterol 2009;136:81

Refractory Celiac Disease
Predictors of Poor Survival

- Multivariate Analysis¹
  - aberrant IELs
  - onset of lymphoma

- Univariate Analysis²
  - albumin ≤ 3.2 g/dl
  - hemoglobin ≤ 11 g/dl
  - age ≥ 65 years
  - aberrant IELs (NS)
  - total villous atrophy (NS)

¹Malamut et al. Gastroenterol 2009;136:81
Refractory Celiac Disease Treatment

- RCD Type I
  - Prednisone
  - Maintenance with azathioprine alone

- RCD Type II
  - No curative therapy
  - Prednisone
  - Cladribine
  - Alemtuzamab
  - Autologous Stem Cell Transplant
  - Parenteral Nutrition often needed

Al-toma, Mulder J Gastrointestin Liver Dis 2007;16:57
Malamut et al. Gastroenterol 2009;136:81

Case

- 74 y.o. Caucasian man
- 2 yrs of diarrhea with wt loss, dehydration
- Duodenal Bx: villous atrophy, ↑IELs
- No celiac serologies obtained
- Treated with gluten-free diet, steroids
- Recurrent diarrhea with steroid taper
- Colonoscopy to TI with biopsies normal
- Gastrin, Chromogranin, VIP, urine 5HIAA normal
Diagnosis and Management

- Genetic Testing Performed
  HLA DQ2, DQ8: Negative
  This is not Celiac Disease!
- Review of Medications: Olmesartan
- Discontinued Olmesartan
- Diarrhea resolved
- Gluten re-introduced into diet

Olmesartan Enteropathy

- Angiotensin II receptor antagonist (ARB)
- Older age group
- Presents as diarrhea, weight loss
- Biopsy looks like CD or Collagenous Sprue
- Negative Celiac Serology
- Unresponsive to a gluten-free diet
- Accounts for 30% non-celiac villous atrophy
- Associated lymphocytic gastritis or colitis
- Resolves with drug removal

Case

- 72 y.o. South American woman
- 2 yrs nausea, vomiting, mild diarrhea, wt loss
- PMH: Autoimmune hemolytic anemia
- Low Hgb, MCV, Zn, Alb, T.P, vit A levels
- W/U:
  - RUQ USG normal
  - Abd CT: ↑spleen, gastric wall thickening
  - Gastric Emptying Study: delayed
- EGD/Colonoscopy: villous atrophy, erosions TI
- EMA negative
Autoimmune Enteropathy

- Rare
- Infants, elderly
- History other autoimmune diseases
- Diarrhea, weight loss
- Autoantibodies
  - Anti-Enterocyte
  - Anti-Goblet Cell
- May involve stomach and colon as well
- No response to a gluten free diet
- Usually requires immunosuppression
  - budesonide, prednisone, others
  - may require PN

Montalto et al. Scan J Gastroenterol 2009;44:1029

Enteropathies

Summary

- Many diseases cause villous atrophy
- Diarrhea, weight loss, and vitamin/mineral deficiencies – expedite evaluation
- Obtain serology (tTG, EMA) to support diagnosis of Celiac Disease before GFD
- In the elderly or GFD unresponsive, think
  - drug [olmesartan, mycophenolate (transplant)]
  - autoimmune
  - occult gluten ingestion if celiac disease
  - tropical sprue if travel to Tropics
Bacterial Overgrowth:  
Getting the Bugs Out

Lawrence R. Schiller, MD, FACG  
Digestive Health Associates of Texas  
Baylor University Medical Center, Dallas

Bacterial Flora of the Gut

• Up to a million trillion ($10^{15}$) bacteria in gut  
  – Only $10^{14}$ human cells in average body  
  – ~500 distinct species identified in colon  
  – Only ~1/3 of bacteria can be cultured  
• Relatively stable populations  
  – Selection of resident bacteria by gut immune system  
• Traditionally viewed as commensals: no great benefit, no great harm
Bacterial Flora of the Gut

- Most bacteria are located in colon
- Bacterial flora in proximal small bowel is relatively sparse (<10^5 bacteria per mL)
- Density of bacteria in distal small bowel is higher (<10^8/mL), but still several orders of magnitude less than in colon
- Low density of bacteria in small intestine facilitates digestion


Effects of Bacterial Overgrowth

- Deconjugation of bile acids
  - Allows absorption of bile acid throughout gut
  - Reduces bile acid concentration below critical micellar concentration → fat malabsorption
- Carbohydrate fermentation
  - Reduces carbohydrate absorption
  - Produces gas
- Interferes with vitamin B\textsubscript{12} absorption
- Mucosal injury
Physiological Suppression of Bacterial Overgrowth

- Very low pH in stomach
- Secretory IgA
- Defensins/other Paneth cell products
- Gastric and small bowel motility
  - Migrating motor complex during fasting
- Ileocecal valve

Settings in which Bacterial Overgrowth is Seen

- Hypochlorhydria due to gastritis or drugs
- IgA deficiency/immunodeficiency states
- Small bowel dysmotility, gastroparesis
  - Diabetes
  - Scleroderma
  - Pseudo-obstruction
- Structural problems
  - Blind loops/postoperative changes
  - Diverticula/strictures/gastrocolic fistulas
Clinical Predictors of SIBO

- 675 patients at Mayo Clinic who had duodenal aspirate for quantitative culture
  - 8% were positive
- Factors associated with (+) culture
  - Older age
  - Steatorrhea
  - Narcotic use
  - IBD, small bowel diverticula, pancreatitis


Old Presentations of Bacterial Overgrowth

- Malabsorption syndrome
  - Diarrhea/steatorrhea
  - Malnutrition
  - Vitamin deficiency states
    - Macrocytic anemia
    - Neuropathy
    - Tetany/osteomalacia
    - Night blindness/dermatitis
- Tropical sprue
New Presentations of Bacterial Overgrowth

- Chronic watery diarrhea
- Irritable bowel syndrome
  - A work in progress
  - Prevalence ranges from 5-80% of IBS patients in different studies (? test artifact)
  - “Chicken vs. egg” (treatment effects)
  - ? More distal location of excess bacterial flora
  - ? Relation to post-infectious state

Improvement in IBS Symptoms 1-10 weeks after completing 10 days of therapy with rifaximin or placebo¹

N=44 (P), 43 (R)
P=0.02

New Presentations of Bacterial Overgrowth

• Other gut disorders\(^1\)
  – ? Inflammatory bowel disease
  – ? Unspecified sprue
  – ? Colorectal cancer

• Extraintestinal disease
  – ? Nonalcoholic fatty liver disease\(^2\)
  – Rosacea

\(^1\)DuPont AW, DuPont HL. Nat Rev Gastroenterol Hepatol 2011;8:523-531.

Diagnosis

• Direct tests
  – Quantitative culture of luminal aspirate

• Indirect tests
  – Products of bacterial metabolism
    • Short chain fatty acid concentration in aspirate
    • Urinary metabolite (4-hydroxyphenylacetic acid)
  – Absorption of exogenous substrate
    • D-xylose tolerance test (serum or urine)
    • Schilling test
Diagnosis

• **Indirect tests**
  – Bile acid deconjugation
    • Endogenous bile acid: unconjugated serum bile acid
    • Exogenous bile acid conjugated to marker
      – Ursodeoxycholic acid—\( p \)-aminobenzoic acid
      – Cholic acid—\( p \)-aminobenzoic acid
  – Breath tests

Breath Tests

• Based on bacterial metabolism of isotopically-labeled conjugated bile acid to isotopically-labeled CO\(_2\) or fermentation of carbohydrate to hydrogen or methane gas
• **Very** dependent on technical factors
  – Dose of substrate administered
  – Collection of expired air for analysis
  – Time-course
  – Interpretation of concentration vs. time graphs\(^1\)

\(^1\)Ghoshal UC. *J Neurogastroenterol Motil* 2011;17:312-317.
Breath Tests

• Additional technical factors
  – 10-20% of individuals do NOT have hydrogen-producing bacteria
    • Simultaneous measurement of methane excretion may compensate for this
  – Analysis of expired air depends on precise methods, fastidious technique; not always reproducible from laboratory to laboratory
  – Increase in concentration that is positive signal is arbitrary (10 or 20 ppm)

Substrates for Breath Tests

• Glucose
  – Absorbed rapidly in proximal jejunum
  – Little substrate available in distal small bowel even with large dose (25 g)

• Xylose
  – Less well absorbed than glucose
  – Tiny doses (1 g) absorbed in proximal intestine
  – Larger doses (25 g) distributed further down gut

GLUCOSE AND XYLOSE ONLY MEASURE PROXIMAL OVERGROWTH
Substrates for Breath Tests

- **Lactulose**
  - Poorly absorbed in small bowel
    - Exposed to entire length of small bowel
    - Most enters colon and exposed to bacteria there
  - Interpretation of H$_2$ concentration—time curve
    - “Double-peak”
    - “Early peak” (<4 hours from ingestion)
    - “High peak” (>50 ppm at any time)
  - Confounding due to rapid transit
    - Independent transit measure: scintigraphy

- **Isotopically-labeled conjugated bile acid**
  - Normally absorbed in terminal ileum
    - Exposed to entire length of gut
    - Little should get to colon if ileal function is normal
      (? Effect of rapid transit/ileal dysfunction)
  - Should pick up distal small bowel bacterial overgrowth, but no “gold standard” to compare
  - Isotopically-labeled CO$_2$ (not H$_2$) is detected
Performance Characteristics of Breath Tests

• Highly variable
• Breath hydrogen vs. quantitative culture
  – Glucose
    • Sensitivity: 27-93%
    • Specificity: 30-86%
  – Lactulose
    • Sensitivity: 17-89%
    • Specificity: 44-100%

Performance Characteristics of Breath Tests

• Isotopically-labeled CO$_2$ vs. quantitative culture
  – D-xylose (1 g dose)
    • Sensitivity: 42-100%
    • Specificity: 59-100%
  – Isotopically-labeled conjugated bile acid
    • Sensitivity: 70%
    • Specificity: 90%
Recommendations for Diagnostic Testing

• For **proximal** small bowel overgrowth
  – Aspirate for quantitative culture
  – Isotopically-labeled 1 g d-xylose breath test
  – Glucose breath hydrogen test
• For **distal** small bowel overgrowth
  – Ideal test not devised
  – Isotopically-labeled bile acid breath test
  – ? Aspiration via double-balloon enteroscopy

Treatment

• Effective antibiotic therapy is key
• Few controlled studies
• Choose agents that kill gram-negative aerobic enteric flora and/or anaerobes
  – Trimethoprim-sulfamethoxazole
  – Amoxicillin
  – Fluoroquinolones
  – Tetracyclines
  – Metronidazole
**Rifaximin**

- Poorly absorbable antibiotic, rifaximin, has been much studied lately
- Currently FDA-approved for treatment of travelers’ diarrhea (200 mg TID X 3 days), hepatic encephalopathy (550 mg BID)
- Doses used in studies: 400-550 mg TID X 7-14 days, ? more is better
- Did better than chlortetracycline for relief of symptoms and breath hydrogen excretion


**Treatment**

- Initial course of treatment → assess response
- Relapse likely because fundamental process (e.g., stasis, immune problem) not addressed by antibiotics, but time to relapse uncertain
- Rotation of antibiotics to avoid resistance advised, but unproven
- Continuous therapy should be avoided
Bile Acid Malabsorption:
When Detergents Are Too Much

Joseph H. Sellin, MD, FACG
Baylor College of Medicine

Bile Acid Diarrhea
BAD, BAD, BAD
Too Much Detergent
or
Too Many Bile Acids?

Joseph H. Sellin MD, FACG
Baylor College of Medicine
Houston, Texas
The Intricacies of BAD

- Enterohepatic Circulation
- Classification of Bile Acid Diarrhea
- Mechanisms of Bile Acid Diarrhea
- Diagnosis
- Treatment
- Unresolved Issues

ENTEROHEPATIC CIRCULATION OF BILE SALTS

Hepatic synthesis from cholesterol by CYP7A1
Conjugated with glycine or taurine
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Hepatic synthesis from cholesterol by CYP7A1
Conjugated with glycine or taurine
Secreted via biliary tree into intestine
Solubilise lipids in micelles for absorption
Reabsorbed in distal intestine:
Active absorption in ileum (conjugated)

Reuptake by hepatocytes and resecreted
ENTEROHEPATIC CIRCULATION OF BILE SALTS

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Conjugated with glycine or taurine
Secreted via biliary tree into intestine
Solubilise lipids in micelles for absorption
Reabsorbed in distal intestine:
  Active absorption in ileum
Reuptake by hepatocytes and resecreted

Bile salts entering the colon cause diarrhea

Colonic Secretion

Stimulation of colonic enterocytes leads to Cl⁻ secretion, H₂O losses

Effect of bile acids on colon
Bile Acids and the Colon

• Chloride Secretion
  – Initially a detergent effect (2-5 mM doses)
  – Low dose, Ca-mediated secretion (1-2 μM doses)
• Increased Motility, Decreased Transit Time
• Epithelial Proliferation

Bile Acids and the Microbiome

• Fecal BAs very different from biliary BAs
• Bacterial deconjugation of taurine/glycine conjugated bile acids
• 7αβ dehydroxylation via bacterial hydrolases
• Primary Bile Acids made in the liver
  – Chenodeoxycholic Acid
  – Cholic Acid
• Secondary Bile Acids from bacterial metabolism
  – Lithocholic Acid
  – Deoxycholic Acid
Diet, Bile Acids, Bugs & Colitis

• Dietary fat promotes changes in host bile acid composition: increased taurine conjugated BA
• Increased availability organic sulfur
• Expansion of a low abundance sulfite reducing *B. wadsworthia*
• Pro-inflammatory TH1 immune response
• Development of colitis in IL 10 -/- mice

BAD: Proof of Principle

• IBAT/ASBT: Apical bile salt transporter
• A3309, IBAT inhibitor
  – Rx for constipation
  – Colonic transit accelerated
  – Looser stool
A Classification of Types of Bile Acid Malabsorption


- **Type 1: Secondary**
  - Ileal resection, ileal disease (Crohn’s), bypass

- **Type 2: Primary**
  - “Idiopathic BA malabsorption (IBAM)”
  - Primary BA Diarrhea (PBAD)

- **Type 3: Miscellaneous associated disorders**
  - Post-cholecystectomy, gastric surgery, chronic pancreatitis, celiac disease, SIBO, radiation enteropathy, microscopic colitis, etc.

Bile Acids and Diarrhea

- Ileal disease/surgery: Makes sense
- Post-GBX: Mechanism???
- IBAM: Mechanism???
Mechanisms of BAD

- Disruption of enterohepatic circulation
  - Congenital deficiency of ileal transporter
  - Ileal resection
  - Ileal disease -> Crohn’s

Post Cholecystectomy Diarrhea

Common -- >10% of patients

- Why?
  - Bile acid malabsorption??
  - Greater resident time in the gut yields greater bacterial dehydroxylation, increasing the “diarrheogenic” bile salts??
  - Decreased colonic transit time
Post-Cholecystectomy Diarrhea

• Bile Acid Malabsorption

• Cholestyramine Works
Increased Fecal Primary Bile Acids in IBS-D

Bowel functions, fecal unconjugated primary and secondary bile acids, and colonic transit in patients with irritable bowel syndrome.

- Total fecal bile acids associated with phenotype (p=0.03); ↑ in IBS-D
- Fecal levels of unconjugated primary UBAs (cholic and chenodeoxycholic acids) ↑ in IBS-D (p<0.01)

Increase in fecal primary bile acids and dysbiosis in patients with diarrhea-predominant irritable bowel syndrome.

- In feces in IBS-D patients:
  - ↑ % of primary bile acid (CA & CDCA)
  - ↓ % of secondary bile acids (DCA)
  - ↑ in E. coli, ↓ in leptum and bifidobacteria

Mechanisms of BAD

- Overflow phenomena?
  - Expanded bile acid pool
  - Limited ileal absorptive capacity overwhelmed
  - Not “true” malabsorption
  - Net result similar: colonic bile acids stimulate chloride secretion
  - Limited evidence
Diagnosing Bile Acid Malabsorption / Diarrhea

- Fecal bile acids
- $^{14}$C-glycocholate breath tests
- $^{75}$SeHCAT retention
- $7\alpha$-hydroxy-4-cholesten-3-one (C4, 7α-C4)
- Therapeutic trials


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**Diagnosis of Bile Acid Malabsorption**

**SeHCAT**

Synthetic $^{75}$Se radiolabelled bile acid analogue


Detected by gamma-camera
Limited radiation exposure
Kinetics similar to taurocholate
Measure of BA retention
7 day retention:
- normal > 15%
- < 10% diagnostic

Available in many European countries
Not available in USA
Abnormal SeHCAT Values in D-IBS

<table>
<thead>
<tr>
<th>Reported SeHCAT value</th>
<th>&lt; 5%</th>
<th>&lt; 10%</th>
<th>&lt; 15%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studies reporting</td>
<td>5</td>
<td>17</td>
<td>7</td>
<td>18</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>429</td>
<td>1,073</td>
<td>618</td>
<td>1,223</td>
</tr>
<tr>
<td>Number abnormal</td>
<td>43</td>
<td>339</td>
<td>163</td>
<td></td>
</tr>
<tr>
<td>% abnormal (95% confidence intervals)</td>
<td>10% (7 – 13)</td>
<td>32% (29 – 35)</td>
<td>26% (23 – 30)</td>
<td></td>
</tr>
<tr>
<td>% response to cholestyramine</td>
<td>96%</td>
<td>80%</td>
<td>70%</td>
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</tr>
</tbody>
</table>


Bile Acid Malabsorption: Frequency of Abnormal SeHCAT

<table>
<thead>
<tr>
<th>SeHCAT retention &lt;10%</th>
<th>Response in these to BA sequestrants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn's with resection</td>
<td>36 / 37 97%</td>
</tr>
<tr>
<td>Crohn's without resection</td>
<td>24 / 44 54%</td>
</tr>
<tr>
<td>Vagotomy / pyloroplasty (+/- cholecystectomy)</td>
<td>15 / 26 58%</td>
</tr>
<tr>
<td>Diarrhoea-predominant IBS</td>
<td>65 / 197 33%</td>
</tr>
</tbody>
</table>

JR Coll Physicians Lond 2000;34:448-451. 304 patients
SeHCAT in Diagnosis of Bile Acid Malabsorption & Prediction of Response to Cholestyramine

Low SeHCAT in proportion of patients with functional diarrhea
Low SeHCAT predicts response to cholestyramine
SeHCAT retention inversely related to faecal bile acids

Idiopathic Bile Acid Malabsorption

- SeHCAT: Only in Europe
  - Consistent increases in bile salt excretion
  - Responds to cholestyramine
- But
  - No change in ileal bile salt transporters
  - Enlarged bile acid pool
  - Increased bile acid synthesis
IBAM: An explanation?

- “Classic” IBAM patients
  - Decreased SeHCAT retention
  - Response to cholestyramine
- Decreased FGF19, increased C4 suggests increased bile acid pool
- Overflow rather than malabsorption
- What controls FGF19 ???

Enterohpetic Circulation

- Intestinal BA’s inhibit hepatic synthesis
- FGF 19
  - Made in intestine
  - Represses Hepatic BA synthesis
- C4: Circulating bile acid intermediate
  - Indicator of overall BA synthesis


FGF19 & Primary Bile Acid Diarrhea

- Bile acid diarrhea:
  - ↓ FGF19
  - ↑ BA synthesis
  - ↑ BA entering colon
  - ↑ Secretory diarrhea
Raised 7aOH-4-Cholesten-3-one (C4) in Patients with Chronic Bile Acid Diarrhea

Fasting blood samples from 17 patients and 19 healthy controls
SeHCAT in 13 patients (all < 8%)
Medians & quartiles
p < 0.001

Reduced FGF19 in Patients with Chronic Bile Acid Diarrhea

Significantly lower FGF19 in patients
p < 0.005
FGF19 in Prospective Groups with Chronic Diarrhea

Significantly lower median fasting FGF19 in patients with primary or secondary BAD compared with chronic diarrhea controls with normal SeHCAT values

Patient Groups

Chronic diarrhoea controls
Primary BAD
Secondary BAD

FGF19 (pg/ml)

0
200
400
600
800
1000

Treatment of Bile Acid Diarrhea

- **Bile acid sequestrants are effective treatments**
  - Bind Bile Salts in intestine
  - Cholestyramine (Questran®) & Colestipol (Colestid®) – powders
  - Colesevelam (Cholestagel®, Wellchol®) – tablets

- **Therapeutic problems**
  - Poor long-term compliance
  - Bloating may worsen
  - Sequestrants can bind other drugs / vitamins
  - Optimal dosing regimes uncertain
  - Titration to individual needs

- Therapeutic trials not necessarily successful
- **Non-specific therapy may also work**
- If the diagnosis is firmly established then the various therapeutic options can be refined to obtain the best clinical response.


FXR Agonists as Treatment for BAD?

- FXR agonists
- Stimulate FGF19
- Inhibit excessive hepatic Bile Acid synthesis
- Reduce colonic secretions / symptoms

BAD: Unresolved Issues

- How much of IBS is due to BAD?
- True Etiology or Epiphenomenon?
  - Primary motility disorder leads to secondary BAD?
  - Associations w/ infections, microscopic colitis, IBS
  - Sometimes transient (stopping rx)
  - BAD and SIBO
- Why does FGF decrease?
- Why do symptoms wax and wane?
BAD Today/BAD Tomorrow

- Bile Acid Diarrhea is a common condition which is poorly recognized
- Diagnostic tests are not widely available
- Treatment with bile acid sequestrants: therapeutic trial
- The role of FGF19 in pathogenesis may help define the primary disorder
- Potential for therapy with FXR agonists?

Altered Bacterial Metabolism?

- Abnormal sulfation abolishes secretory effect of BA’s in a subset of pediatric constipation.
- Increase in unconjugated primary BAs in d-IBS
- Lower unconjugated primary BAs in c-IBS
Additional Roles of FGF 19?

- Serum FGF19 levels increased following bariatric surgery
- Diabetic patients who went into remission had the greatest increases ($P<0.001$)
- Diabetic patients in remission also had the greatest increases in total bile acids
- Different relationship than BAD?
  - Cholic acid has been inversely related with insulin resistance
    - Argyropoulos G. 2013; ADA meeting

Diagnostic Dilemmas

- Fecal Bile Acid Assays are difficult, require timed stool collections
- Breath Test is not specific (double peak)
- C4 elevated with ETOH, chronic liver disease, elevated Triglycerides
- FGF 19 altered in cholestatic liver disease, obesity.
FGF19 is a Negative Regulator of Hepatic Bile Acid Synthesis

FGF19 in humans
FGF15 in mice

Could defective FGF19 signalling cause primary BA diarrhea?

Mechanism of Bile Acid Diarrhea

- Excess bile acids in colon
  - Unabsorbed by the small intestine
  - Increased bile acid synthesis
- Bacterial transformation of bile acids
  - Deconjugation
  - Dehydroxylation
- Stimulation of colonic secretion
  - Anion secretion
  - Watery stool
  - Motility changes

FGF19 in Different Types of Bile Acid Diarrhea

Figure 2
Chronic diarrhea due to excessive bile acid synthesis and not defective ileal transport: a new syndrome of defective FGF19 release.

Systemic Review of SeHCAT in Chronic Diarrhea


<table>
<thead>
<tr>
<th>Author (date)</th>
<th>Number of patients tested</th>
<th>Number of positive patients (%SeHCAT retention &lt;10%)</th>
<th>% BAM-positive patients (confidence interval)</th>
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<tbody>
<tr>
<td>Merrick (1965)</td>
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<td>Scharrett (1966)</td>
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<td>6</td>
<td>46 (9-61)</td>
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<tr>
<td>Scharrett (1967)</td>
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<td>12</td>
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<tr>
<td>Williams (1991)</td>
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<td>29</td>
<td>22 (16-28)</td>
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<td>Ford (1992)</td>
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<td>20 (12-31)</td>
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<tr>
<td>Galantola (1993)</td>
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<td>Elshefai (1993)</td>
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<td>46 (26-67)</td>
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<td>Scharrett (1994)</td>
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<td>339</td>
<td>32 (29-35)</td>
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</table>

Table 4. Studies reporting patients with 7d SeHCAT retention <10%